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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
|---|---|---|---|
| 09/410,462 | 10/01/99 | WILLIAMS | A |

HM22/0915

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| SORBELLO,E | |
| **ART UNIT** | **PAPER NUMBER** |
| 1633 | 7 |

**DATE MAILED:** 09/15/00

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

File copy

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/410,462 | WILLIAMS ET AL. | |
| | Examiner | Art Unit | |
| | Eleanor Sorbello | 1633 | |

*-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

**Status**

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) 1-28 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-28 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

**Attachment(s)**

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6 .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☒ Other: *See Continuation Sheet* .

Continuation of 20. Other: 1)Notice to Comply and 2) Raw Sequence Error Report Entered as Paper No. 5.

## DETAILED ACTION

### *Sequence Compliance*

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

A complete response to this Official Action must include compliance with the sequence Rules as well as addressing the issues listed further herein.

### *Claim Rejections - 35 USC § 112*

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

3. Claims 1-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while **being enabling for (I)** a replication competent adenovirus comprising a mutation in the E1A-CR2 region, wherein said adenovirus is dl922/947, or dl1107 or pm928, wherein mutation lies in the conserved region 2 of E1A gene comprising a deletion or substitution of one or more amino acids between position 122 to 129; wherein said mutation lies in the retinoblastoma gene product binding region of

the adenovirus; **(II)** *in vitro* methods for substantially and selectively killing dividing endothelial or cancer cells compared to quiescent cells or non dividing endothelial cells in a mixed cell population of dividing(or cancer cells) and non-dividing or quiescent cells comprising contacting cell population wherein adenovirus is dl922/947 or dl11107 or pm928; **(III)** method for selectively and substantially reducing tumor size by the intratumoral injection of said adenoviral mutant dl922/947 or dl107 or pm928, in nu/nu mice; **does not reasonably provide enablement** for any of the following *in vivo* methods in any context by the administration of one of the said viruses in a cell population comprising dividing and quiescent cells, such as (i) method for substantially and selectively killing dividing cells, and/or (ii) killing dividing cells with less killing in quiescent endothelial cells, and/or (iii) selectively killing dividing endothelial cells and cancer cells compared to quiescent cells and/or (iv) controlling angiogenesis in an animal comprising administration of the said virus. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are directed to the following: (I) methods: (a) for substantially and selectively killing dividing cells in a cell population comprising dividing and quiescent cells, by contacting the cell population with a replication competent adenovirus comprising a mutation in the E1A region wherein RB binding is prevented from occuring; and allowing sufficient time for infection of the cell population to take place, wherein dividing cells are cancer cells or endothelial cells, and/or quiescent cells are endothelial cells; wherein mutation lies in E1A-CR2 region wherein deletion or

substitution lies between amino acids 111 through 129; wherein and/or adenovirus is dl922/947 or dl1107 or pm928. (b) for killing dividing cells with substantially less killing of quiescent endothelial cells, by contacting cell population with replication competent adenovirus, wherein mutant adenovirus replicates to higher titers in dividing cells than wild type adenovirus, thereby killing dividing cells; (c) for substantially and selectively killing dividing endothelial cells and cancer cells compared to quiescent endothelial cells, by contacting cell population comprising 3 cell types with replication competent adenovirus with said mutation;(d) for controlling angiogenesis in an animal by killing dividing microvascular endothelial cells, comprising administering said mutant adenovirus; (II) pharmaceutical compositions comprising the said adenoviral mutants in a physiological solution; and (III) compositions comprising the said adenoviral mutants.

The specification teaches construction of said adenoviruses comprising the E1A region in the conserved regions (CR) of E1A responsible for the binding of pRB ( such as p107 and p130). The specific CR2 gene deletions present in dl922/947 and dl11107 and point mutation in pm928 are also taught in the specification. The specification teaches the construction of mutant adenoviruses with the ability to replicate as a percentage of the wild-type adenoviral replication in dividing cells and cancer cells. The specification specifically teaches the replication ability of dl922/947 compared to the wild type adenovirus in (a) quiescent cells *in vitro* (b) proliferating non-immortalized human microvascular endothelial cells such as Q-MVEC and P-MVEC *in vitro* ; and (c) C33A cervical carcinoma cells and HLaC laryngeal carcinoma cells *in vitro*.

The specification also teaches increased cytopathic ability of the said mutants dl922/947 versus the wild-type adenovirus on tumor cells *in vitro* in cell lines such as H2009 non-small cell lung carcinoma cells and HLaC laryngeal carcinoma cells, U2OS osteosarcoma cells infected with the said mutant adenovirus(dl11107).

The specification teaches an intratumoral injection with the said mutant adenovirus in a nude mouse-human xenograft model. Tumors in the nude mouse animal model were previously induced by human colon tumor cells (RKO.RC 7.14) or human laryngeal tumor cells (HLaC). The specification taught that $10^8$ pfu of dl922/947 or wild type adenovirus injected daily for 5 consecative days, resulted in a significant tumor shrinkage.

The specification states formulations and compositions comprising about $10^3$ to $10^{15}$ or more adenoviral particles in aqueous suspensions. The specification also states a variety of aqueous solutions such as water, saline, glycine and the like that are known in the art of the formulation of compositions. However, it is unclear if a person skilled in the art can simulate the formulation of any composition with regards to the breadth of the claimed invention with expectation of success.

The specification lacks guidance as to the breadth of the claims regarding the mutant adenovirus of the instant invention, and its ultimate functioning in a *in vivo* method of (a) substantially and selectively killing dividing cells, (b) substantially killing less quiescent cells and (c) a method for controlling angiogenesis in an animal. The specification gives guidance for the construction of said mutants, but the claims encompass any *in vivo* administration of said mutant, which may not necessarily

reflect similar functioning even though the virus is administered. Therefore, the statement of rejection indicates that the specification is enabled for an adenoviral virus comprising an E1 deletion comprising a mutation in the RB protein binding region of the conserved region 2 (CR2); for *in vitro* methods for substantially and selectively killing dividing cells and cancer cells with considerably less killing of quiescent or non-dividing cells in a mixed cell population comprising dividing endothelial or cancer cells and non-dividing or quiescent cells, by contacting the cell population with said mutant adenovirus; and for an *in vivo* method of tumor reduction by the intratumoral injection of the mutant virus of the instant invention.

In view of the claims drawn to methods of introducing a virus to an individual, wherein the virus delivers a mutated RB binding molecule into the cells of an individual, wherein the said virus substantially and selectively kills dividing cells as compared to quiescent cells of the individual, the claims are directed broadly to any *in vivo* gene delivery method, which may include gene therapy and/or cancer gene therapy.

The specification prophetically considers *in vivo* applications such as the administration of the virus to cells for substantially or selectively killing dividing cells as compared to quiescent cells, by the administration of the mutant virus of the instant invention, or for controlling angiogenesis. There is no specific teaching which indicate applicants are enabled for any in vivo therapy which include administration of the viruses except for the intratumor administration of the virus to a nude mouse with tumors. This method reads specifically on gene therapy where a mutated gene is

administered to therapeutically modify the existing gene resulting in reduction in tumor size specifically not killing other quiescent cells in the vicinity of the tumor.

The pharmaceutical composition claims are being examined under enablement because the language "pharmaceutical" implies that the vector of claims provides for *in vivo* applicability particularly for treatment, but such is not enabled as are argued herein.

Dang et al. in 1999, in a report summarizing the status of gene therapy, found human gene therapy to be an immature science with limited understanding of gene regulation and disease models for preclinical studies. (see page 471, paragraph 1). They also noted that it is not possible to predict results from one animal model to another, as was seen in experiments with nude mice and that with dogs. (see page 471, col. 2 , paragraph 2).

Eck et al. taught that the delivery of recombinant DNA has been a central issue in gene transfer *in vivo* . For instance, numerous factors complicate the art of gene delivery *in vivo* which have not been shown to be overcome by routine experimentation. Eck et al. explains, the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.); the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced; the stability of the mRNA produced, the amount and stability of the protein produced; and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the

vector used, the protein being produced, and the disease being treated. [See Eck et al., ¶ bridging pages 81-82.]

None of these unpredictable factors discussed by Dang and Eck were specfically addressed in applicants disclosure. The instant specification does not teach the site of delivery, composition and quantities of adenovirus to be used in order to measure significant and substantial killing of dividing cells as opposed to quiescent cells in any situation in vivo except by prophetic consideration. Further it is unclear that from cell culture and one *in vivo* example that one could support the broad claims, in view of the unpredictability in the art.

This experiment was conducted using nude mice that have a defective immune system. The immune system of non-nude mice would normally be activated when a virus is introduced, rejecting the virus. Hence it is not clear if a person skilled in the art will be able to extrapolate results from the experiment performed in the instant invention to any *in vivo* experiment and reasonably expect success. Furthermore, Gura et al. taught that xenograft tumors do not behave like naturally occurring tumors in humans, as they do not spread to other tissues, and therefore drugs tested with xenograft tumors appeared effective but worked poorly in humans.(see Gura et al. page 1041 col. 2, paragraph 3).

In view of this, it would require undue experimentation for one skilled in the art to be able to practice the claimed invention for substantially and selectively killing dividing cells as compared to quiescent cells, and as a method for controlling angiogenesis by administering a mutant adenovirus to any cell *in vivo* in any context. Since, one

skilled in the art cannot readily anticipate the results predicted for any *in vivo* context to which the claimed invention pertains based on the guidance provided in applicant's disclosure, one skilled in the art would necessarily consider such subject matter to be unpredictable.

Therefore, considering the broad claim drawn to a method for substantially and selectively killing dividing cells *in vivo*, with less killing of quiescent cells; and a method for controlling angiogenesis; the specification is enabled for *in vitro* applications with the said viruses and for the intratumoral injection of said viruses for tumor reduction in nude mice, but is not enabled for any *in vivo* application wherein dividing cells are selectively and substantially killed. In order for one skilled in the art to practice the invention as claimed one would have to engage in undue experimentation in order to be able to administer the virus of the instant invention via any route of administration, and in any composition, to be able to selectively and substantially kill dividing cells, by the administration of the mutant virus.

In conclusion, given the nature of the invention, the state of the art, the demonstrated lack of predictability of the art, the lack of guidance set forth, the breadth of the claims, the quantity of experimentation required, one of skill in the art could not use the invention *in vivo* in any context without undue experimentation.

### *Claim Rejections - 35 USC § 103*

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 21-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bischoff et al. (U.S. Pat. No. 6,080,578) in view of Whyte, P. et al., Jelsma T.N. et al. and Moran et al.

The claims are directed to compositions and pharmaceutical compositions comprising mutant adenoviruses wherein the mutation is in the E1A region of the adenovirus wherein the RB protein binds, thereby eliminating the binding ability of the RB to the adenovirus. The claims further recite specific adenoviruses with a mutation or deletion in the E1A region such as dl922/947 wherein amino acids 122 to 129 are deleted; and dl1107 wherein amino acids 111 to 123 are deleted; and Pm928 wherein a single amino acid substitution from cysteine to glycine in position 124.

The pharmaceutical composition claims are being examined only to the extent that they read on compositions per se, because pharmaceutical compositions per se do not impart any particular or new feature other than the components of the vector.

Bischoff et al. discloses adenoviruses comprising an E1A locus encoding a mutant E1A protein that lacks a CR1 and/or CR2 domain therefore being incapable of binding RB (see abstract; col. 3, lines 66-67 ; col. 4 lines 1-19 and lines 35-40).

Bishoff does not expressly disclose the specific adenoviral mutants namely dl922/947 wherein amino acids 122 to 129 are deleted; and dl1107 wherein amino acids

111 to 123 are deleted; and Pm928 wherein there is a single amino acid substitution from cysteine to glycine in position 124.

Whyte et al. Jelsma et al. and Moran et al. disclose adenoviral mutants such as dl922/947 (wherein amino acids 122 to 129 are deleted); and dl1107 (wherein amino acids 111 to 123 are deleted); and Pm928 (wherein there is a single amino acid substitution from cysteine to glycine in position 124) respectively wherein these mutations in the E1 region resulted in a total loss of transforming ability of the adenovirus.

It would have been obvious for one of skill in the art at the time of the invention to include the adenoviral mutants as taught by Whyte et al., Jelsma et al. and Moran due to the loss of transforming ability of these adenoviruses, (See Whyte abstract lines 6-7; see Jelsma abstract line 4; and Moran abstract line 7), in an invention that encompasses the limitation whereby neoplastic cells are preferentially killed due to the inability of the mutated E1A protein to bind the RB protein, thereby freeing the RB protein to function as a tumor suppressor.

Bischoff et al. disclose that sterile compositions and pharmaceutically acceptable carriers or excipients which include water buffered water, 0.4% saline or 0.3% glycine and the like can be used, to deliver mutant adenoviral constructs. (See Bischoff , Col 17, lines 1-5).

One or ordinary skill in the art would have been motivated to combine the teachings of Bischoff, Whyte, Jelsma and Moran whereby adenoviruses comprising an E1A locus encoding a mutant E1A protein that lacks a CR1 and/or CR2 domain thereby

being incapable of binding RB in compositions comprising the adenovirus (see Bischof abstract) to include such limitations as was taught by Whyte, Jelsma and Moran so that more adenoviruses are available for selectively killing neoplastic or dividing cells in a mixed cell population.

One of ordinary skill in the art would have been reasonably assured of success in killing neoplasic/dividing cells *in vitro* by the administration of adenoviral mutants including those taught by Whyte, Jelsma and Moran which had limitations that were encompassed by the broad category of adenovrial mutants as disclosed by Bischoff et al.(in that they all had mutations in the E1A region which prevented the binding the RB protein) and since they all had the ability to prevent neoplastic cells from dividing.

***Conclusion***

6. Claims 1-28 are rejected.

7. Any inquiry concerning this communication should be directed to Eleanor Sorbello, who can be reached at (703)-308-6043. The examiner can normally be reached on Mondays-Fridays from 6.30 a.m. to 3.00 p.m. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

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